III. Remarks

A. Amendments to the Claims and Formal Matters

Claims 62, 66-71 and 75-86 are pending in the application. Claims 1-61 were previously canceled. Claims 84 and 86 were previously withdrawn from consideration by the Examiner. With this amendment, Applicant amends claims 62 and 75 and cancels claims 84 and 86. Upon entry of these amendments, claims 62, 66-71, 75-83 and 85 will be pending and under active consideration.

Claim 62 is amended to recite "said mutations" in light of the two separate mutations recited in the claim and to recite an isolated "human" IFNAR2 polypeptide.

Claim 75 is amended to recite "any one of claims 62 or 66-71" in light of the cancellation of claims 63-65.

Applicant has amended paragraph [0026] at page 7 of the specification as amended under 37 C.F.R. § 1.121(b)(3), to refer to SEQ ID NO: 1.

In view of the application as originally filed providing support for each of the amendments made herein, Applicant respectfully submits that no new matter has been added.

B. Patentability Rejections

1. 35 U.S.C. §112, First Paragraph – Written Description

At page 3 of the Final Office Action, the Examiner maintains the rejection of claims 62-65, 67-83 and 85 under 35 U.S.C. §112 as allegedly failing to comply with the written description requirement. Examiner alleges that Applicant has described only one species of IFNAR2 polypeptides and is therefore not entitled to the genus. Applicant amends the claims to be directed to human IFNAR2 polypeptides as described in the application as originally filed. Accordingly, Applicant respectfully requests that the rejection for lack of written description support be reconsidered and withdrawn.

At page 6 of the Final Office Action, Examiner maintains his rejection of claims 62-65, 67-83 and 85 as allegedly failing to comply with the written description requirement, based on his allegation that the specification does not demonstrate possession of alternatively spliced membrane bound or cytoplasmic forms of IFNAR.

Applicant respectfully disagrees with Examiner. The specification, at paragraph [0006] discloses that IFNAR2 β_S and β_L subunits have "identical" extracellular domains. Further, at paragraph [0008], the specification discloses that transcripts for the soluble p40 IFNAR2 "encompass almost the entire extracellular domain of the IFNAR2 subunit." Each of these alternatively spliced IFNAR2 forms have been shown to bind IFNβ (see paragraphs cited *supra*). Thus, each alternatively spliced IFNAR2 isoform contains the entire (or nearly the entire) extracellular domain and binds IFNβ. Thus, one of ordinary skill in the art would understand that because the extracellular domain of IFNAR2 is the portion that interacts with IFNβ, that the teachings of the instant invention apply to each alternately spliced IFNAR2 isoform and accordingly will understand that Applicant possessed this aspect of the invention at the time the Application was filed. Based on the foregoing, Applicant respectfully requests reconsideration and withdrawal of the rejection for lack of written description.

2. 35 U.S.C. §112, First Paragraph – Enablement

a. Claims 62-65, 67-83 and 85

At page 6 of the Final Office Action, the Examiner maintains the rejection of claims 62, 66-71 and 75-82 under 35 U.S.C. §112 for an alleged lack of enablement. The Examiner bases this rejection on his allegation that the claims "broadly encompass isolated and mutated polypeptide sequences of numerous variants of the type I IFN receptors, such as membrane bound, cytoplasmic or soluble forms." Applicant respectfully reminds Examiner that the claims are directed to IFNAR2 polypeptides and not to "type 1 IFN receptors" generally. Applicant amends the claims to be directed to "human" IFNAR2 polypeptides as described in the application as originally filed. Further, as mentioned supra, every identified IFNAR2 variant is taught by the specification to contain all (or nearly all) of the extracellular domain of IFNAR2, through which interaction with IFNβ is mediated. Accordingly, Applicant respectfully requests that the rejection for lack of enablement be reconsidered and withdrawn.

b. Claims 83 and 85

At page 7 of the Final Office Action, the Examiner maintains the rejection of claims 83 and 85 under 35 U.S.C. §112 for an alleged lack of enablement. The Examiner

bases the rejection on the allegation that the use of an effective amount of the claimed polypeptide for treating an autoimmune disease or multiple sclerosis is not enabled "absent a strong showing by Applicant." The Examiner maintains the rejection of claims 83 and 85 because "[t]he specification fails to provide a description of what constitutes a therapeutically effective amount of a composition comprising a therapeutic effective amount of a composition comprising the IFNAR2 mutated polypeptide." Applicant respectfully disagrees. The specification, at paragraph [0076] defines a "therapeutically effective amount" as an amount that, when administered, "results in modulation of the biological activity of IFNβ." A variety of factors upon which "[t]he dosage administered...may vary" are taught by the specification as well.

The skilled artisan understands that the amount of mutated IFNAR2 polypeptide which constitutes a "therapeutically effective" amount depends upon the application. Where the application is improved bioavailability of administered IFNβ, paragraph [0098] of the specification teaches that "considerably lower amounts [of mutated IFNAR2 than of wild type IFNAR2] will be required to accomplish its carrier activity" consequently allowing administration of lower amounts of IFNβ. For this application, a therapeutically effective amount of mutated IFNAR2 is an amount sufficient to result in "some portion of [IFNb] available for curative activity (20%) and some amount of [IFNb] bound to the [mutated IFNAR2] and protected (about 80%)" (*see* paragraph [0030]). For the claimed IFNAR2 mutant, the specification teaches that the desired result is achieved at a concentration of "about 0.24 nM...equivalent to 6 μg/Kg)" of claimed mutated IFNAR2 polypeptide (see paragraph [0033]).

Where the desired result is a decrease in the bioavailability of endogenous IFNβ, a routine application of the law of mass action allows the ordinary artisan to calculate a concentration of mutated IFNAR2 that when administered, will be sufficient to bind a given percentage of IFNβ. Selecting the appropriate effective amount of a composition for a particular patient is well within the skill of the ordinary artisan and may be determined without undue experimentation. Accordingly, Applicant respectfully requests that the rejection for lack of enablement be reconsidered and withdrawn.

3. 35 U.S.C. §103(a)

a. Claims 62-76

At page 8 of the Office Action, the Examiner maintains the rejection of claims 62-76 under 35 U.S.C. §103(a) over Piehler *et al.* ("Piehler"). The Examiner continues to allege that the claims are obvious because Piehler, as characterized by the Examiner, (i) describes the effects of individual mutations at positions His 78 and Asp 100; (ii) provides the motivation to simultaneously mutate His 78 and Asp 100; and (iii) provides a reasonable expectation of success. Applicant respectfully disagrees. Application respectfully submits that the Examiner has failed to take into account secondary considerations of non-obviousness.

Secondary considerations, such as unexpected results, must be considered in every case in which they are present. *See MPEP* § 2141. As stated in the instant specification at page 29, lines 14-17 and shown in Table 4, each of the claimed double mutants H78A/N100A, H78A/N100D and H78A/N100H demonstrates a synergistic effect of the combined mutations on the affinity of the polypeptide to IFNβ compared to single mutations at H78 and N100. Piehler fails to teach or suggest such a result. According to MPEP § 716.02(a), a demonstration of synergism is sufficient to overcome a *prima facie* case of obviousness where the results obtained are greater than those which could have been expected from the prior art to an unobvious extent and the results are of significant, practical advantage.

According to Piehler, substituting alanine for histidine at position 78 (H78A) and asparagine at position 100 (N100A) of IFNAR2 decreases the dissociation rate constant for IFNβ by almost twofold and fourfold respectively. The change in the free energy of binding IFNβ is disclosed as -1.9 kJ/mole for H78A and -3.1 kJ/mole for N100A. According to Piehler, and as the ordinary artisan understands, the change in free energy for a multiple mutant should equal the sum of energy changes of the individual single mutations. Thus, for the claimed double mutant H78A/N100A, a change in free energy of binding IFNβ of 5.0 kJ/mole is the expected result. According to the formula (5) of Piehler, this corresponds to an expected 8-fold increase in affinity of H78A/N100A for IFNβ. The specification, however, teaches that H78A/N100A exhibits a 50-fold increase in affinity – more than six-times the expected result. Applicant respectfully disagrees

with Examiner that Piehler discloses such an increase. Examiner removed the cited statement in Piehler from its proper context. The statement cited by Examiner, in context, reads: "the phenotype of a H78, N100 double mutation in ifnar2 [should] have about 20-fold tighter binding for IFNβ compared to IFNα2" (emphasis added). Thus, Piehler's statement is not comparing the affinity of H78A/N100A for IFNβ to that of wild type IFNAR2; rather, Piehler's statement compares the relative affinity of H78A/N100A for IFNβ and IFNα. In light of Piehler's disclosure that the affinity of H78A for IFNα is reduced more than two-fold, a nearly 20-fold tighter binding is the expected result in the absence of synergy between the mutations.

Moreover, the aforementioned evidence is disclosed in the instant specification at paragraph [0014]. According to *In re Soni*, 54 F.3d 746, 750, 34 USPQ.2d 1684, 1687 (Fed. Cir. 1995), where the evidence relied upon by Applicant to show unexpected results is in the specification to which Applicant has attested, a declaration according to 37 C.F.R. 1.132 is unnecessary. In light of the unexpected, claimed synergistic increase, no indication of which is disclosed by Piehler and which could not have been obvious to the ordinary artisan, Applicant respectfully requests that the rejection for obviousness be reconsidered and withdrawn.

b. Claims 77-81

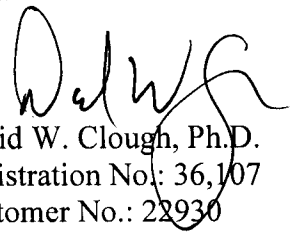
At page 9 of the Final Office Action, the Examiner maintains his rejection of claims 77-81 under 35 U.S.C. §103(a) over Piehler and Campbell *et al.* ("Campbell"). As discussed above, Piehler fails to teach or suggest the synergistic effect of the claimed double mutant H78A/N100A. Campbell does nothing to remedy the defect of Piehler. Accordingly, Applicant respectfully requests that the rejection for obviousness be reconsidered and withdrawn.

C. Conclusion

In view of the above amendments and remarks, Applicant respectfully submits that the instant application is in good and proper order for allowance and early notification to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite prosecution of the instant application, the Examiner is encouraged to call the undersigned at the number listed below.

Respectfully submitted,

HOWREY LLP

By: 
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